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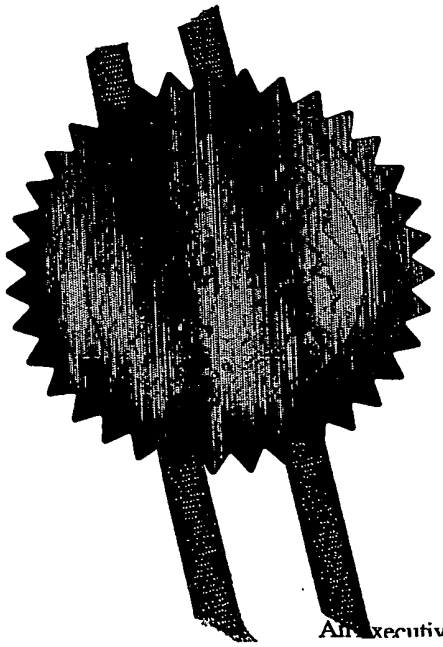

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Dated 20 February 2004

Patents Form 1/77

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17JUL03 E823125-1 000245
P01/7700 0.00-0316656.8

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

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1.	Your reference	4-33282P1/HO 83
		16 JUL 2003
2.	Patent application number *(The Patent Office will fill in this part)*	0316656.8
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	NOVARTIS AG LICHTSTRASSE 35 4056 BASEL SWITZERLAND
	Patent ADP number *(if you know it)*	
	If the applicant is a corporate body, give the country/state of its incorporation	SWITZERLAND 7125487005
4.	Title of invention	Organic Compounds
5.	Name of your agent *(If you have one)*	
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	Craig McLean Novartis Pharmaceuticals UK Limited Patents and Trademarks Wimblehurst Road Horsham West Sussex RH12 5AB
	Patents ADP number *(if you know it)*	07181522002

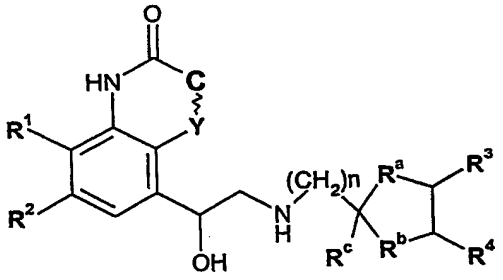
6.	If you are declaring priority from one ore more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of filing (day/month/year)
7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application		Number of earlier application	Date of filing (day/month/year)
8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *(see note (d))*	Yes		

DUPLICATE

ORGANIC COMPOUNDS

This invention relates to organic compounds, their preparation and use as pharmaceuticals.

The invention provides in one aspect a compound of formula I



I

in free or salt or solvate form, where

-C~Y- denotes $-CH_2-CH_2-$, -CH=CH- or $-CH_2-O-$;

one of R^1 and R^2 is hydroxy and the other is hydrogen;

n is an integer from 0 to 4;

R^a and R^b are independently $-CR^5R^6-$, $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$, -O-, $-CH_2-O-$, $-CH_2-O-CH_2-$, -S-, -SO-, $-SO_2-$, $-CH_2-S-$, $-CH_2-CH_2-S-$, $-CH_2-SO-$, $-CH_2-SO_2-$ or a bond;

R^c is hydrogen or C_1-C_{10}-alkyl optionally substituted by C_1-C_{10}-alkoxy, C_7-C_{15}-aralkyloxy, a C_5-C_{15}-carbocyclic group or by a 5- or 6-membered heterocyclic group wherein at least one of the ring atoms is nitrogen, oxygen or sulphur;

or when R^b is $-CR^5R^6-$, R^c and R^b form a C_5-C_{15}-carbocyclic group;

R^3 and R^4 form a 5- or 6-membered heterocyclic ring wherein at least one of the ring atoms is nitrogen, oxygen or sulphur, that ring being optionally substituted by halo, oxo, cyano, hydroxy, carboxy, aminocarbonyl, nitro, a C_5-C_{15}-carbocyclic group, C_7-C_{15}-aralkyl, C_1-C_{10}-alkyl optionally substituted by C_3-C_{10}-cycloalkyl, or C_1-C_{10}-alkoxy optionally substituted by C_3-C_{10}-cycloalkyl; and

R^5 and R^6 are independently hydrogen, C_1-C_{10}-alkyl or C_1-C_{10}-alkoxy, either of which being optionally substituted by a C_5-C_{15}-carbocyclic group.

Terms used in this specification have the following meanings:

"Optionally substituted" as used herein means the group referred to can be substituted at one or more positions by any one or any combination of the radicals listed thereafter.

"C_1-C_{10}-alkyl" as used herein denotes straight chain or branched alkyl. Preferably C_1-C_{10}-alkyl is C_1-C_4-alkyl.

"C_1-C_{10}-alkoxy" as used herein denotes straight chain or branched alkoxy. Preferably C_1-C_{10}-alkoxy is C_1-C_4-alkoxy.

"C_3-C_{10}-cycloalkyl" as used herein denotes cycloalkyl having 3 to 10 ring carbon atoms, for example a monocyclic group such as a cyclopropyl, which can be substituted by one or more, usually one or two, C_1-C_4-alkyl groups, or a bicyclic group such as bicycloheptyl or bicyclooctyl. Preferably C_3-C_{10}-cycloalkyl is C_3-C_6-cycloalkyl, especially cyclohexyl.

"C_6-C_{10}-aryl" as used herein denotes a monovalent carbocyclic aromatic group that contains 6 to 10 carbon atoms and which may be, for example, a monocyclic group such as phenyl or a bicyclic group such as naphthyl. Preferably C_6-C_{10}-aryl is C_6-C_8-aryl, especially phenyl.

"C_7-C_{15}-aralkyl" as used herein denotes alkyl, for example C_1-C_5-alkyl as hereinbefore defined, substituted by C_6-C_{10}-aryl as hereinbefore defined. Preferably C_7-C_{15}-aralkyl is C_7-C_{10}-aralkyl such as phenyl-C_1-C_4-alkyl, but especially benzyl.

"C_7-C_{15}-aralkyloxy" as used herein denotes alkoxy, for example C_1-C_5-alkoxy as hereinbefore defined, substituted by C_6-C_{10}-aryl as hereinbefore defined. Preferably C_7-C_{15}-aralkyloxy is C_7-C_{10}-aralkyloxy such as phenyl-C_1-C_4-alkoxy, for example benzyloxy.

"C_5-C_{15}-carbocyclic group" as used herein denotes a carbocyclic group having 5 to 15 ring carbon atoms, for example a monocyclic group, either aromatic or non-aromatic, such as cyclopentyl, cyclohexyl or phenyl, any of which can be substituted by one or more, usually one or two, C_1-C_4-alkyl groups, or a bicyclic group such as bicyclooctyl, indanyl or indenyl, again any of which can be substituted by one or more, usually one or two, C_1-C_4-alkyl groups . Preferably the C_5-C_{15}-carbocyclic group is a C_5-C_{10}-carbocyclic group, for example C_3-C_{10}-cycloalkyl or phenyl, but especially cyclohexyl or phenyl.

"Halo" or "halogen" as used herein denotes a element belonging to group 17 (formerly group VII) of the Periodic Table of Elements, which may be, for example, fluorine, chlorine, bromine or iodine. Preferably halo or halogen is bromine.

"5- or 6- membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur" as used herein may be, for example, pyrrole, pyrrolidine, pyrazole, imidazole, triazole, tetrazole, thiadiazole, isothiazole, thiophene, oxadiazole, pyridine, furan, oxazole, isoxazole, pyrazine, pyridazine, pyrimidine, piperazine, morpholino, triazine, oxazine or thiazole. Preferred 5- or 6- membered heterocyclic rings include pyrrolidine, pyrrole, pyrazole, furan, thiophene, pyridine and pyrazine. The 5- or 6- membered heterocyclic ring can be unsubstituted or substituted. Preferred substituents on the heterocyclic ring include halo, oxo, cyano, hydroxy, carboxy, aminocarbonyl, nitro, a C_5-C_{15}-carbocyclic group, C_7-C_{15}-aralkyl, C_1-C_{10}-alkyl optionally substituted by C_3-C_{10}-cycloalkyl, or C_1-C_{10}-alkoxy optionally substituted by C_3-C_{10}-cycloalkyl. Especially preferred substituents on the ring include oxo, C_7-C_{15}-aralkyl and C_1-C_{10}-alkyl optionally substituted by C_3-C_{10}-cycloalkyl.

Throughout this specification and in the claims that follow, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

Preferred compounds of the present invention are compounds of formula I where
-C~Y- is -CH=CH-;
one of R^1 and R^2 is hydroxy and the other is hydrogen;
n is 0 or 1;
R^a and R^b are both methylene;
R^c is hydrogen; and
R^3 and R^4 form a 5- or 6-membered heterocyclic ring wherein at least one of the ring atoms is nitrogen, oxygen or sulphur, that ring being optionally substituted by oxo, C_7-C_{15}-aralkyl or C_1-C_{10}-alkyl optionally substituted by C_3-C_{10}-cycloalkyl.

Especially preferred compounds of the present invention are compounds of formula I where
-C~Y- is -CH=CH-;
one of R^1 and R^2 is hydroxy and the other is hydrogen;
n is 0 or 1;
R^a and R^b are both methylene;
R^c is hydrogen; and

R^3 and R^4 form a 5- or 6-membered heterocyclic ring wherein at least one of the ring atoms is nitrogen, oxygen or sulphur, that ring being optionally substituted by oxo, C_7-C_{10}-aralkyl or C_1-C_4-alkyl optionally substituted by C_3-C_6-cycloalkyl.

The compounds of formula (I) are capable of forming acid addition salts, particularly pharmaceutically acceptable acid addition salts. Pharmaceutically acceptable acid addition salts of the compound of formula I include those of inorganic acids, for example, hydrohalic acids such as hydrofluoric acid, hydrochloric acid, hydrobromic acid or hydroiodic acid, nitric acid, sulfuric acid, phosphoric acid; and organic acids such as formic acid, acetic acid, propionic acid, butyric acid, benzoic acid, o-hydroxybenzoic acid, p-hydroxybenzoic acid, p-chlorobenzoic acid, diphenylacetic acid, triphenylacetic acid, 1-hydroxynaphthalene-2-carboxylic acid, 3-hydroxynaphthalene-2-carboxylic acid, aliphatic hydroxy acids such as lactic acid, citric acid, tartaric acid or malic acid, dicarboxylic acids such as fumaric acid, maleic acid or succinic acid and sulfonic acids such as methanesulfonic acid or benzenesulfonic acid, and unsaturated monobasic aromatic acids such cinnamic acid, 4-methoxy cinnamic acid or 4-methyl cinnamic acid. These salts may be prepared from compounds of formula I by known salt-forming procedurés.

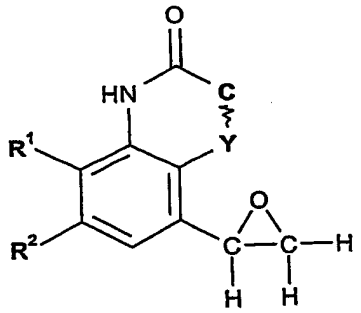
Compounds of formula I which contain acidic, e.g. carboxyl groups, are also capable of forming salts with bases, in particular pharmaceutically acceptable bases such as those well known in the art; suitable such salts include metal salts, particularly alkali metal or alkaline earth metal salts such as sodium, potassium, magnesium or calcium salts, or salts with ammonia or pharmaceutically acceptable organic amines or heterocyclic bases such as ethanolamines, benzylamines or pyridine. These salts may be prepared from compounds of formula I by known salt-forming procedures.

In those compounds where there is an asymmetric carbon atom the compounds exist in individual optically active isomeric forms or as mixtures thereof, e.g. as racemic or diastereomeric mixtures. The present invention embraces individual optically active R and S isomers as well as mixtures, e.g. racemic or diastereomeric mixtures, thereof.

Specific especially preferred compounds of the invention are those described hereinafter in the Examples.

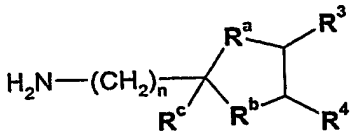
The present invention also provides a process for the preparation of compounds of formula I in free or salt or solvate form. They can be prepared by a process comprising:

(i) (A) for the preparation of compounds of formula I reacting a compound of formula II



II

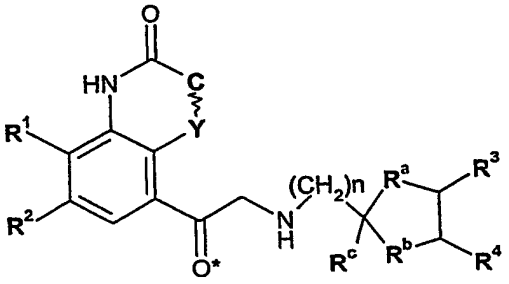
or a protected form thereof wherein -C-Y-, R^1 and R^2 are as hereinbefore defined, with a compound of formula III



III

or a protected form thereof wherein R^a, R^b, R^c, R^3, R^4 and n are as hereinbefore defined;

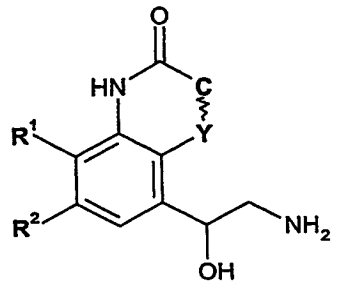
(B) reducing a compound of formula IV



IV

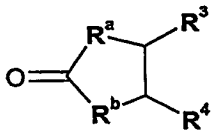
or a protected form thereof wherein -C~Y-, R^a, R^b, R^c, R^1, R^2, R^3, R^4 and n are as hereinbefore defined, to convert the indicated keto group into -CH(OH); or

(C) for the preparation of compounds of formula I where R^c is hydrogen and n is 0, reacting a compound of formula V



V

or a protected form thereof wherein -C~Y-, R^1 and R^2 are as hereinbefore defined, with a compound of formula VI



VI

or a protected form thereof wherein R^a, R^b, R^3 and R^4 are as hereinbefore defined; and

(ii) recovering the resultant compound of formula I in free or salt or solvate form.

Process variant (A) may be carried out using known procedures for reacting epoxides with amines or analogously as hereinafter described in the Examples. The reaction is conveniently carried out without a solvent or in an inert solvent, for example an organic solvent such as N,N'-dimethylformamide (in the presence of a silylating agent such as N,O-bis(trimethyl-silyl)-acetamide) or 2-methoxyethyl ether. The reaction temperature is conveniently from 25°C to 200°C, preferably from 80°C to 190°C. The temperature may be achieved by conventional heating or by microwave irradiation.

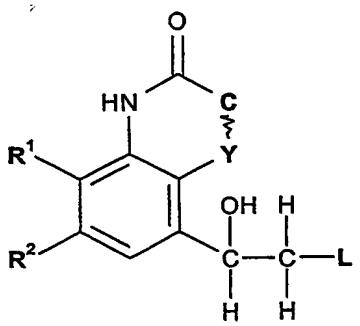
Process variant (B) may be carried out using conventional methods, for example by hydrogenation using a suitable catalyst such as Pd/C or by reaction with sodium borohydride or a borane reducing agent under conventional conditions.

Process variant (C) may be carried out using known procedures for reacting amino alcohols with ketones or analogously under reductive amination conditions as hereinafter described in the Examples. The reaction is conveniently carried out using a borohydride salt under acidic conditions, for example sodium triacetoxyborohydride and acetic acid, and using an organic solvent, for example 1,2-dichloromethane, as described in *J. Org. Chem.* 1996, 61, 3849. The reaction temperature is conveniently from 0° C to 25° C, preferably room temperature.

Compounds of formula I in free form may be converted into salt form, and vice versa, in a conventional manner. The compounds in free or salt form can be obtained in the form of hydrates or solvates containing a solvent used for crystallisation. Compounds of formula I can be recovered from reaction mixtures and purified in a conventional manner. Isomers, such as enantiomers, may be obtained in a conventional manner, e.g. by fractional crystallisation or asymmetric synthesis from correspondingly asymmetrically substituted, e.g. optically active, starting materials.

Compounds of formula II are known compounds or can be prepared by processes analogous to those used for the preparation of the known compounds, for example the procedures described in *J. Med. Chem.* 1987, 30, 1563.

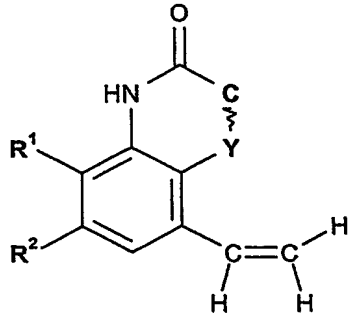
Compounds of formula II in which the carbon atom of the epoxide ring that is attached to the phenyl group is chiral may be prepared from a compound of formula VII



VII

or a protected form thereof where -C~Y-, R^1 and R^2 are as hereinbefore defined and L is a leaving atom or group, as described in international patent application WO 95/25104 or analogously as hereinafter described in the Examples.

Compounds of formula II may alternatively be prepared by epoxidation of a compound of formula VIII

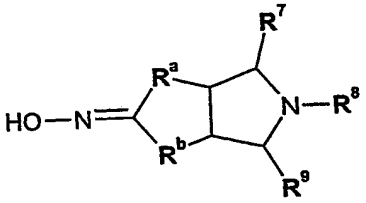


VIII

ed form thereof -C~Y-, R^1 and R^2 are as hereinbefore defined, using
ventional procedures.

Compounds of formula III are known or may be prepared by methods analogous to those used for the preparation of the known compounds, for example the procedures described by R. Helmers in *J. fuer Practische Chemie*, 1971, 313, 31; M. H. Palmer et al in *Tetrahedron* 1978, 34, 1015; and J. G. Berger et al in *J. Org. Chem.* 1970, 35, 3122. The amine group may be protected by known methods, for example using an amine-protective group described in Protective Groups in Organic Synthesis, T. W. Greene, P.G.M. Wuts, John Wiley & Sons Inc, Third Edition, 1999, preferably benzyl or trifluoroacetyl.

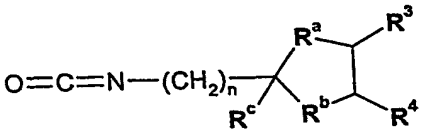
Compounds of formula III where R^3 and R^4 form a pyrrolidine ring, R^c is hydrogen and n is 0 may be prepared by reacting a compound of formula IX



IX

or a protected form thereof where R^a and R^b are as hereinbefore defined and R^7, R^8 and R^9 are each independently hydrogen, halo, oxo, cyano, hydroxy, carboxy, aminocarbonyl, nitro, a C_5-C_{15}-carbocyclic group, C_7-C_{15}-aralkyl, C_1-C_{10}-alkyl optionally substituted by C_3-C_{10}-cycloalkyl, or C_1-C_{10}-alkoxy optionally substituted by C_3-C_{10}-cycloalky or C_1-C_{10}-alkyl, with a reducing agent. The reaction may be carried out using known procedures for converting oximes to amines, for example as described by Fischer et al in *J. Het. Chem.* 1991, 28, 1677 or analogously as hereinafter described in the Examples. The reaction is conveniently carried out by hydrogenation in an inert solvent, for example ethanol, preferably in the presence of an acid such as hydrochloric acid and a noble metal catalyst such as platinum oxide. The reaction temperature is conveniently from 0 to 100°C, preferably from 25 to 40°C.

Compounds of formula III where R^3 and R^4 form a 5- or 6-membered heterocyclic ring may be prepared by reacting a compound of formula X

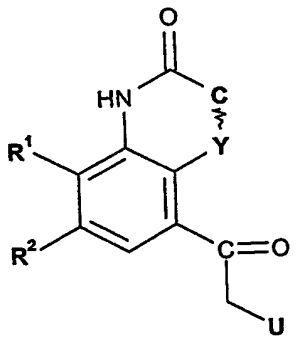


X

or a protected form thereof wherein R^a, R^b, R^c, R^3, R^4 and n are as hereinbefore defined,

with a strong acid in aqueous solution. The reaction may be carried out using known procedures for converting isocyanates to amines, for example as described by Huebner et al in *J. Org. Chem.* 1962, 27, 4465 or analogously as hereinafter described in the Examples. The reaction is conveniently from 80°C to reflux temperature.

Compounds of formula IV are novel compounds which may be prepared by reaction of a compound of formula XI



XI

or a protected form thereof where -C~Y-, R^1 and R^2 are as hereinbefore defined and U is a halogen atom, preferably chlorine or bromine, with a compound of formula III as hereinbefore defined. The reaction may be carried out using conventional procedures, for example those described by Yoshizaki et al, *J. Med. Chem* 1976, 19, 1138, or analogously as hereinafter described in the Examples.

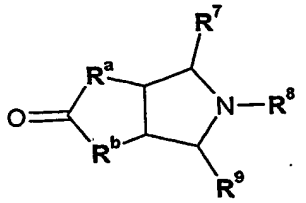
Compounds of formula V are known or may be prepared by reacting a compound of formula II where Y, R^1 and R^2 are as hereinbefore defined with ammonia or a protected form thereof or azide using known methods for reacting epoxides with amines or analogously as hereinafter described in the Examples. Where a compound of formula II is reacted with azide, a reduction step is subsequently required to yield the compound of formula V.

Compounds of formula VI are known or may be prepared by known procedures such as those described in *Liebigs Ann. Chem.* 1985, 435.

Compounds of formula VII are known or may be prepared by methods analogous to those used for the preparation of known compounds, for example those used in the Examples hereinafter.

Compounds of formula VIII are known or may be prepared by known procedures.

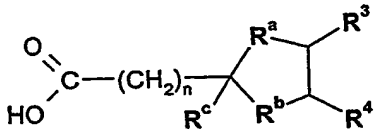
Compounds of formula IX may be prepared by reacting a compound of formula XII



XII

or a protected form thereof where R^a, R^b, R^7, R^8 and R^9 are as hereinbefore defined, with hydroxylamine or preferably a salt thereof. The reaction may be carried out using known procedures for converting ketones to oximes, for example as described by Davis et al in *J. Org. Chem.* 1989, 54, 2021, or analogously as hereinafter described in the Examples. The reaction is conveniently carried out in a solvent, for example a mixture of ethanol and water, preferably in the presence of an inorganic base such as sodium acetate. The reaction temperature is conveniently from 80°C to reflux temperature.

Compounds of formula X may be prepared by converting a compound of formula XIII

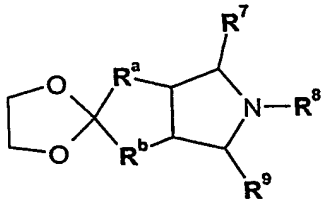


XIII

or a protected form thereof wherein R^a, R^b, R^c, R^3, R^4 and n are as hereinbefore defined, to the corresponding acyl-azide, for example by treating with ethyl chloroformate and triethylamine, and then subjecting the acyl azide to thermolysis in an inert solvent such as toluene at a temperature from 50-100°C. The reaction may be carried out using known procedures for converting carboxylic acids to isocyanates, for example by way of a Curtius rearrangement as described in *J. Org. Chem.* 1962, 27, 4465, or analogously as hereinafter described in the Examples.

Compounds of formula XI are known or may be prepared by known procedures, for example those disclosed in United States patent specification US 4460581 and German patent specification DE 3134590.

Compounds of formula XII may be prepared by reacting a compound of formula XIV

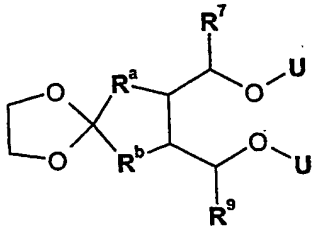


XIV

or a protected form thereof where R^a ,R^b, R^7, R^8 and R^9 are as hereinbefore defined, with an aqueous acid, for example hydrochloric acid. The reaction may be carried out using known procedures for converting dioxolanes to ketones, or analogously as hereinafter described in the Examples. The reaction is conveniently carried out in an organic inert solvent, for example acetone. The reaction temperature is conveniently from ambient to reflux temperature.

Compounds of formula XIII may be prepared by the procedure described in international patent application WO 99/02517, or analogously as hereinafter described in the Examples. When n is 0 those compounds may be prepared from the corresponding bis(halo-alkyl) substituted heterocycle, such as those disclosed in *Org. Process Res. Dev.* 2002, 6, 938, using the procedure that is also described in international patent application WO 99/02517, or analogously as hereinafter described in the Examples.

Compounds of formula XIV may be prepared by reacting a compound of formula XV



XV

or a protected form thereof where R^a, R^b, R^7 and R^9 are as hereinbefore defined and U is a C_1-C_8-alkyl when R^7 and R^9 are both oxo or U is a C_1-C_8-alkyl-sulfonyl group when R^7 and R^9 are both other than oxo, with a compound of formula XVI

$$H_2N—R^8 \qquad \text{XVI}$$

where R^8 is as hereinbefore defined. The reaction may be carried out using known procedures for reacting carboxylic esters or sulfonic esters with amines, for example when U is a C_1-C_8-alkyl that described by Gais et al in *J. Org. Chem.* 1989, 54, 5115, or when U is an C_1-C_8-alkyl-sulfonyl group that described by Guzikowski et al in *J. Med. Chem.* 2000, 43, 984, or analogously as hereinafter described in the Examples. The reaction is conveniently carried out in an organic inert solvent, for example acetone. The reaction temperature is conveniently from ambient to reflux temperature.

Compounds of formula XV are known or may be prepared by known procedures, for example when U is a C_1-C_8-alkyl that described by Gais et al in *J. Org. Chem.* 1989, 54, 5115, or analogously as hereinafter described in the Examples. When U is a C_1-C_8-alkyl-

sulfonyl group those compounds can be prepared by reacting the corresponding alcohol, such as those disclosed in *Tet. Lett.* 2002, 43, 4947, with the relevant alkyl-sulfonyl halide, for example using the procedure disclosed in "March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure", M. B. Smith and J. March, Fifth Edition, 2001, page 587 or analogously as hereinafter described in the Examples.

Compounds of formula XVI are known or may be prepared by known procedures. Where desired, the protection of any reactive group may be carried out at any appropriate stage in the above processes. The protecting group is suitably one used conventionally in the art and may be introduced and removed using conventional procedure. For example, when a hydroxy group is protected by a benzyl group, the latter may be removed by catalytic hydrogenation in the presence of palladium on charcoal using conventional procedures, such as those used hereinafter in the Examples.

Compounds of formula I in free, salt or solvate form are useful as pharmaceuticals. Accordingly the invention also provides a compound of formula I in free, salt or solvate form for use as a pharmaceutical. The compounds of formula I in free, salt or solvate form, hereinafter referred to alternatively as "agents of the invention", have good β_2-adreno-receptor agonist activity. The β_2 agonist activity, onset of action and duration of action of the agents of the invention may be tested using the guinea pig tracheal strip in vitro assay according to the procedure of R.A. Coleman and A.T. Nials, *J. Pharmacol. Methods* 1989, 21, 71. The binding potency and selectivity for the β2-adrenoreceptor relative to the β1-adrenoreceptor can be measured by a classical filtration binding assay according to the procedure of Current Protocols in Pharmacology (S. J. Enna (editor-in-chief) et al, John Wiley & Son, Inc, 1998), or by cAMP determination in cells expressing β2- or β1-adrenoceptor, according to the procedure of B. January et al, *Brit. J. Pharmacol.* 1998, 123, 701.

The agents of the invention commonly have a rapid onset of action and have a prolonged stimulating action on the β_2-adrenoreceptor, compounds of the Examples hereinbelow having K_i (β_2) values of the order of 0.1 to 1000 nM, having durations of action of the order of 1 to greater than 12 hours. Many of the compounds have binding selectivities for the β_2-adrenoreceptor relative to the β_1-adrenoreceptor from 1.5 to 500. For example, the compound of Example 5 has β_2 and β_1 binding potencies, measured by a classical filtration binding assay, represented by K_i values (β_2/β_1) (in μM) of 0.121/0.380.

Having regard to their β_2 agonist activity, the agents of the invention are suitable for use in the treatment of any condition which is prevented or alleviated by activation of the β_2-adrenoreceptor. In view of their long acting selective β_2 agonist activity, the agents of the invention are useful in the relaxation of bronchial smooth muscle and the relief of bronchoconstriction. Relief of bronchoconstriction can be measured in models such as the in vivo plethysmography models of Chong et al, *J. Pharmacol. Toxicol. Methods* 1998, 39, 163, Hammelmann et al, *Am. J. Respir. Crit. Care Med.*, 1997, 156, 766 and analogous models.

The agents of the invention are therefore useful in the treatment of obstructive or inflammatory airways diseases. In view of their long duration of action, it is possible to administer the agents of the invention once-a-day in the treatment of such diseases. In another aspect, agents of the invention commonly exhibit characteristics indicating a low incidence of side effects commonly encountered with β_2 agonists such as tachycardia, tremor and restlessness, such agents accordingly being suitable for use in on demand (rescue) treatment as well as prophylactic treatment of obstructive or inflammatory airways diseases.

Treatment of a disease in accordance with the invention may be symptomatic or prophylactic treatment. Inflammatory or obstructive airways diseases to which the present invention is applicable include asthma of whatever type or genesis including both intrinsic (non-allergic) asthma and extrinsic (allergic) asthma. Treatment of asthma is also to be understood as embracing treatment of subjects, e.g. of less than 4 or 5 years of age, exhibiting wheezing symptoms and diagnosed or diagnosable as "wheezy infants", an established patient category of major medical concern and now often identified as incipient or early-phase asthmatics. (For convenience this particular asthmatic condition is referred to as "wheezy-infant syndrome".)

Prophylactic efficacy in the treatment of asthma will be evidenced by reduced frequency or severity of symptomatic attack, e.g. of acute asthmatic or bronchoconstrictor attack, improvement in lung function or improved airways hyperreactivity. It may further be evidenced by reduced requirement for other, symptomatic therapy, i.e. therapy for or intended to restrict or abort symptomatic attack when it occurs, for example anti-inflammatory (e.g. corticosteroid) or bronchodilatory. Prophylactic benefit in asthma may in particular be apparent in subjects prone to "morning dipping". "Morning dipping" is a recognised asthmatic syndrome, common to a substantial percentage of asthmatics and

characterised by asthma attack, e.g. between the hours of about 4 to 6 am, i.e. at a time normally substantially distant from any previously administered symptomatic asthma therapy.

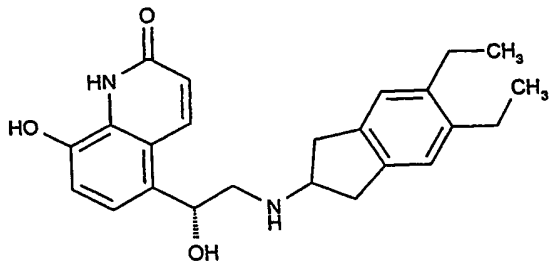
Other inflammatory or obstructive airways diseases and conditions to which the present invention is applicable include adult/acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary or airways disease (COPD or COAD), including chronic bronchitis, or dyspnea associated therewith, emphysema, as well as exacerbation of airways hyperreactivity consequent to other drug therapy, in particular other inhaled drug therapy. The invention is also applicable to the treatment of bronchitis of whatever type or genesis including, e.g., acute, arachidic, catarrhal, croupus, chronic or phthinoid bronchitis. Further inflammatory or obstructive airways diseases to which the present invention is applicable include pneumoconiosis (an inflammatory, commonly occupational, disease of the lungs, frequently accompanied by airways obstruction, whether chronic or acute, and occasioned by repeated inhalation of dusts) of whatever type or genesis, including, for example, aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis.

Having regard to their β_2 agonist activity, the agents of the invention are also useful in the treatment of a condition requiring relaxation of smooth muscle of the uterus or vascular system. They are thus useful for the prevention or alleviation of premature labour pains in pregnancy. They are also useful in the treatment of chronic and acute urticaria, psoriasis, allergic conjunctivitis, actinitis, hay fever, and mastocytosis.

The agents of the invention are also useful as co-therapeutic agents for use in combination with other drug substances such as anti-inflammatory, bronchodilatory, antihistamine or anti-tussive drug substances, particularly in the treatment of obstructive or inflammatory airways diseases such as those mentioned hereinbefore, for example as potentiators of therapeutic activity of such drugs or as a means of reducing required dosaging or potential side effects of such drugs. An agent of the invention may be mixed with the other drug substance in a fixed pharmaceutical composition or it may be administered separately, before, simultaneously with or after the other drug substance. Accordingly the invention includes a combination of an agent of the invention as hereinbefore described with an anti-inflammatory, bronchodilatory, antihistamine or anti-tussive drug substance, said agent of the invention and said drug substance being in the same or different pharmaceutical

composition. Such anti-inflammatory drugs include steroids, in particular glucocorticosteroids such as budesonide, beclamethasone, fluticasone, ciclesonide or mometasone or steroids described in WO 0288167, WO 0212266, WO 02100879 or WO 0200679 (especially those of Examples 3, 11, 14, 17, 19, 26, 34, 37, 39, 51, 60, 67, 72, 73, 90, 99 and 101), LTB4 antagonists such as those described in US 5451700, LTB4 antagonists such as those described in US 5451700, LTD4 antagonists such as montelukast and zafirlukast, PDE4 inhibitors such as Ariflo® (GlaxoSmith Kline), Roflumilast (Byk Gulden),V-11294A (Napp), BAY19-8004 (Bayer), SCH-351591 (Schering-Plough), Arofylline (Almirall Prodesfarma), PD189659 (Parke-Davis), AWD-12-281 (Asta Medica), CDC-801 (Celgene) and KW-4490 (Kyowa Hakko Kogyo) and A2a agonists such as those described in EP 1052264, EP 1241176, WO 0023457, WO0077018, WO 0123399, WO 0160835, WO 0194368, WO 0200676, WO 0222630, WO 0296462, WO 0127130, WO 0127131, WO 9602543, WO 9602553, WO 9828319, WO 9924449, WO 9924450, WO 9924451, WO 9938877, WO 9941267, WO 9967263, WO 9967264, WO 9967265, WO 9967266, WO 9417090, EP 409595A2 and WO 0078774 and A2b antagonists such as those described in WO 02/42298. Such bronchodilatory drugs include anticholinergic or antimuscarinic agents, in particular ipratropium bromide, oxitropium bromide and tiotropium bromide.

The agents of the invention are also useful as co-therapeutic agents for use in combination other beta-2 adrenoceptor agonists, for example as a rescue medication. Suitable beta-2 adrenoceptor agonists include salbutamol, terbutaline, salmeterol and, especially, formoterol and pharmaceutically acceptable salts thereof, and compounds (in free or salt or solvate form) of formula I of PCT International patent publication No. WO 00/75114, which document is incorporated herein by reference, preferably compounds of the Examples thereof, especially a compound of formula



and pharmaceutically acceptable salts thereof.

Co-therapeutic antihistamine drug substances include cetirizine hydrochloride, acetaminophen, clemastine fumarate, promethazine, loratidine, desloratidine, diphenhydramine and fexofenadine hydrochloride.

Combinations of agents of the invention and steroids, PDE4 inhibitors, A2a agonists, A2b agonists or LTD4 antagonists may be used, for example, in the treatment of COPD or, particularly, asthma. Combinations of agents of the invention and anticholinergic or antimuscarinic agents, PDE4 inhibitors, A2a agonists, A2b agonists, dopamine receptor agonists or LTB4 antagonists may be used, for example, in the treatment of asthma or, particularly, COPD.

In accordance with the foregoing, the present invention also provides a method for the treatment of an obstructive or inflammatory airways disease which comprises administering to a subject, particularly a human subject, in need thereof a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore described. In another aspect, the invention provides a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore described for use in the preparation of a medicament for the treatment of an obstructive or inflammatory airways disease.

The agents of the invention may be administered by any appropriate route, e.g. orally, for example in the form of a tablet or capsule; parenterally, for example intravenously; topically to the skin, for example in the treatment of psoriasis; intranasally, for example in the treatment of hay fever; or, preferably, by inhalation, particularly in the treatment of obstructive or inflammatory airways diseases.

In a further aspect, the invention also provides a pharmaceutical composition comprising a compound of formula I in free form or in the form of a pharmaceutically acceptable salt or solvate thereof, optionally together with a pharmaceutically acceptable diluent or carrier therefor. Such compositions may be prepared using conventional diluents or excipients and techniques known in the galenic art. Thus oral dosage forms may include tablets and capsules. Formulations for topical administration may take the form of creams, ointments, gels or transdermal delivery systems, e.g. patches. Compositions for inhalation may comprise aerosol or other atomizable formulations or dry powder formulations.

When the composition comprises an aerosol formulation, it preferably contains, for example, a hydro-fluoro-alkane (HFA) propellant such as HFA134a or HFA227 or a mixture of these, and may contain one or more co-solvents known in the art such as ethanol (up to 20% by weight), and/or one or more surfactants such as oleic acid or sorbitan trioleate, and/or one or more bulking agents such as lactose. When the composition comprises a dry powder formulation, it preferably contains, for example, the compound of formula I having a particle diameter up to 10 microns, optionally together with a diluent or carrier, such as lactose, of the desired particle size distribution and a compound that helps to protect against product performance deterioration due to moisture. When the composition comprises a nebulised formulation, it preferably contains, for example, the compound of formula I either dissolved, or suspended, in a vehicle containing water, a co-solvent such as ethanol or propylene glycol and a stabiliser, which may be a surfactant.

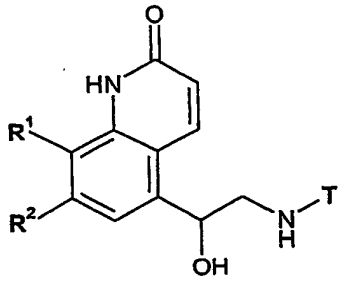
The invention also includes (A) a compound of formula I as hereinbefore described in free form, or a pharmaceutically acceptable salt or solvate thereof, in inhalable form; (B) an inhalable medicament comprising such a compound in inhalable form together with a pharmaceutically acceptable carrier in inhalable form; (C) a pharmaceutical product comprising such a compound in inhalable form in association with an inhalation device; and (D) an inhalation device containing such a compound in inhalable form.

Dosages employed in practising the invention will of course vary depending, for example, on the particular condition to be treated, the effect desired and the mode of administration. In general, suitable daily dosages for administration by inhalation are of the order of from 1 to 5000 μg.

The invention is illustrated by the following Examples.

Examples

Especially preferred compounds of formula I are also compounds of formula XVII

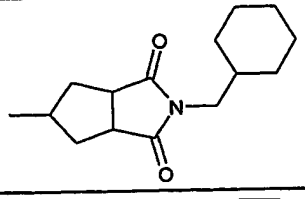
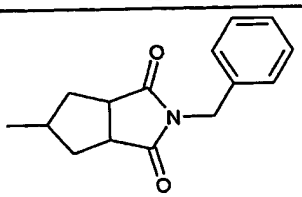
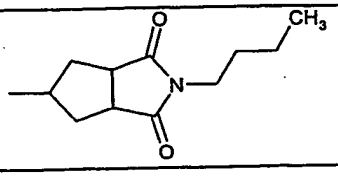


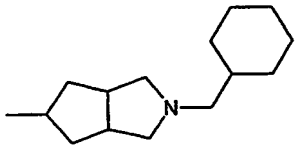
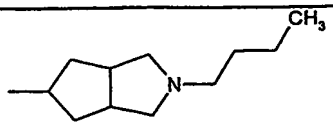
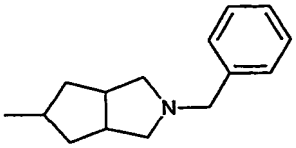
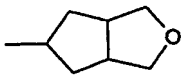
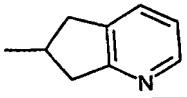
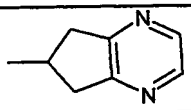
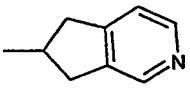
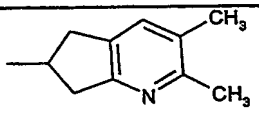
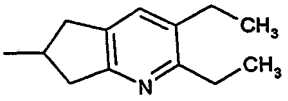
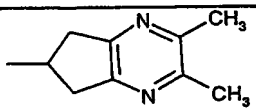
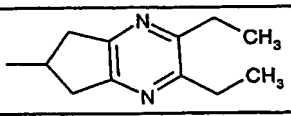
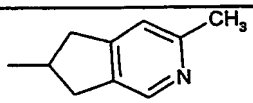
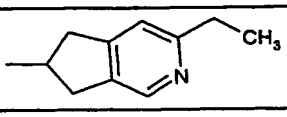
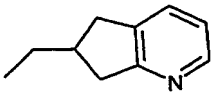
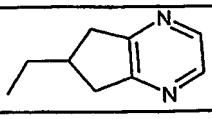
XVII

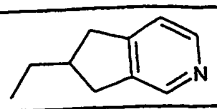
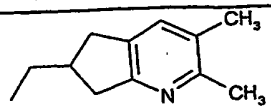
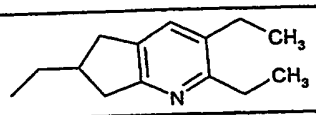
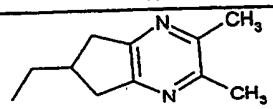
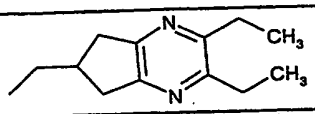
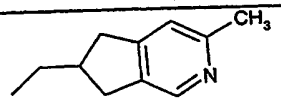
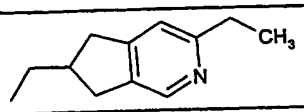
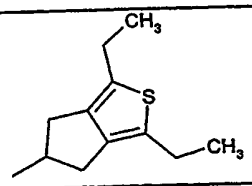
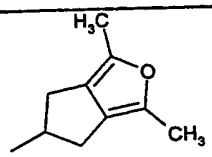
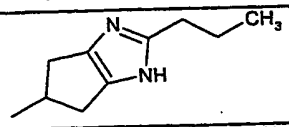
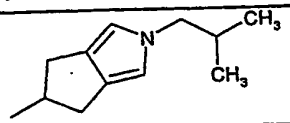
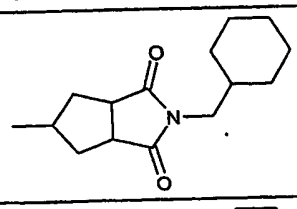
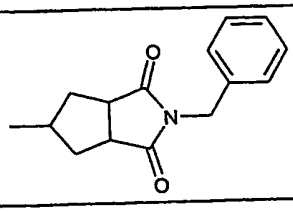
wherein T is as shown in the following table, the method of preparation being described hereinafter.

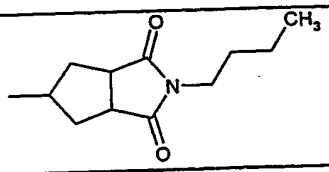
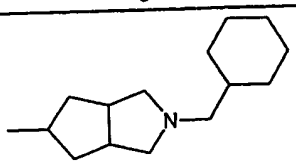
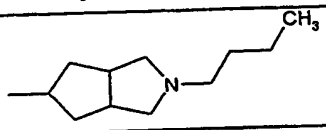
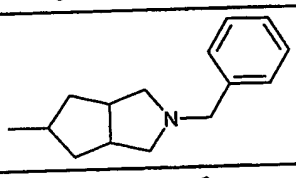
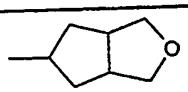
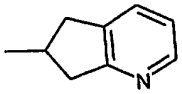
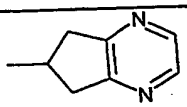
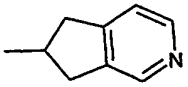
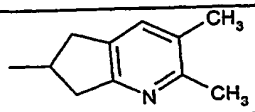
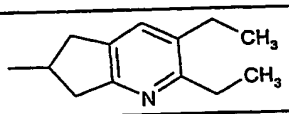
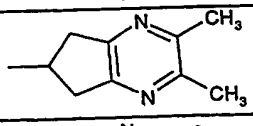
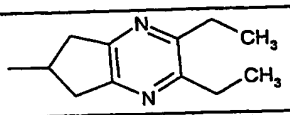
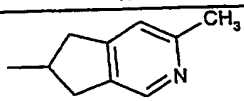
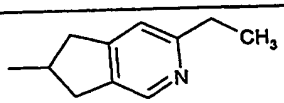
1H NMR spectra are recorded at 400 MHz in $CDCl_3$ unless otherwise noted and 13C NMR spectra are recorded at 100MHz. Mass spectra are obtained under electrospray ionisation conditions with LC gradient elution of 5% to 95% acetonitrile-water in the presence of 0.1% formic acid. Preparative LCMS is conducted on a Phenomenex Luna C18 column (50 x 21.2 mm, 10 µM particle size).

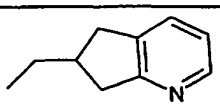
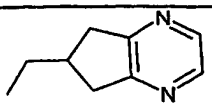
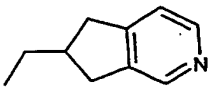
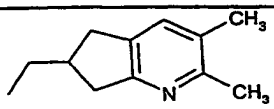
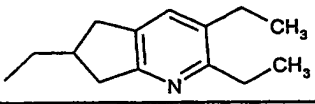
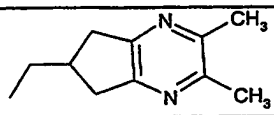
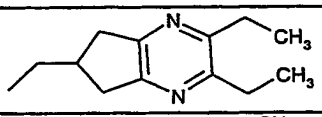
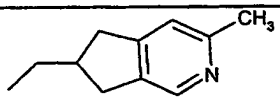
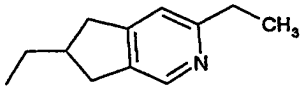
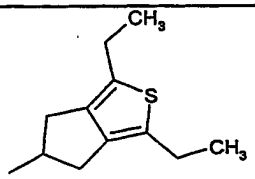
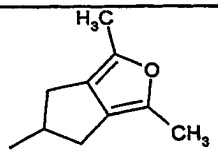
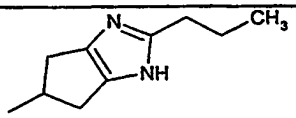
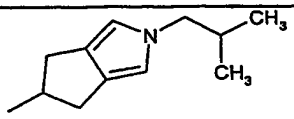
TABLE I

Ex	R^1	R^2	T	MH^+
1	-OH	-H		454
2	-OH	-H		-
3	-OH	-H		-

4	-OH	-H		-
5	-OH	-H		-
6	-OH	-H		-
7	-OH	-H		-
8	-OH	-H		-
9	-OH	-H		-
10	-OH	-H		-
11	-OH	-H		-
12	-OH	-H		-
13	-OH	-H		-
14	-OH	-H		-
15	-OH	-H		-
16	-OH	-H		-
17	-OH	-H		-
18	-OH	-H		-

19	-OH	-H		-
20	-OH	-H		-
21	-OH	-H		-
22	-OH	-H		-
23	-OH	-H		-
24	-OH	-H		-
25	-OH	-H		-
26	-OH	-H		-
27	-OH	-H		-
28	-OH	-H		-
29	-OH	-H		-
30	-H	-OH		-
31	-H	-OH		-

32	-H	-OH		-
33	-H	-OH		-
34	-H	-OH		-
35	-H	-OH		-
36	-H	-OH		-
37	-H	-OH		-
38	-H	-OH		-
39	-H	-OH		-
40	-H	-OH		-
41	-H	-OH		-
42	-H	-OH		-
43	-H	-OH		-
44	-H	-OH		-
45	-H	-OH		-

46	-H	-OH		-
47	-H	-OH		-
48	-H	-OH		-
49	-H	-OH		-
50	-H	-OH		-
51	-H	-OH		-
52	-H	-OH		-
53	-H	-OH		-
54	-H	-OH		-
55	-H	-OH		-
56	-H	-OH		-
57	-H	-OH		-
58	-H	-OH		-

Example 1

(3aS,5R,6aR)-2-Cyclohexylmethyl-5-[R-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]tetrahydrocyclopenta[c]pyrrole-1,3-dione and (3aS,5S,6aR)-2-cyclohexyl-methyl-5-[R-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]tetra-hydrocyclopenta[c]pyrrole-1,3-dione

A mixture of (7S,8R)-1,4-dioxaspiro[4.4]nonane-7,8-dicarboxylic acid dimethyl ester (*J Org Chem*, 1989, 54, 5115; 1.0 g, 4.09 mmol) and benzylamine (6 ml) is heated in a sealed tube at 195°C for 16 hours. The benzylamine is evaporated and the residue purified by flash chromatography, eluting with 2:1 isohexanes-ethyl acetate (EtOAc) to afford (3aS,6aR)-2-benzylspiro[tetrahydrocyclopenta[c]pyrrole-5(1H), 2'-[1,3]dioxolane]-1,3-dione, MH+ 288

1M aqueous hydrochloric acid (3 ml) is added portionwise to a refluxing solution of (3aS,6aR)-2-benzylspiro[tetrahydrocyclopenta[c]pyrrole-5(1H), 2'-[1,3]dioxolane]-1,3-dione (0.265 g, 0.92 mmol) in acetone (20 ml). The reaction is heated for 16 hours, the solvent evaporated and the residue partitioned between dichloromethane and water. The organic phase is washed with brine, dried ($MgSO_4$) and evaporated. The crude product is purified by flash chromatography, eluting with neat dichloromethane to afford (3aS,6aR)-2-benzyl-tetrahydrocyclopenta[c]pyrrole-1,3,5-trione, MH+ 244.

Sodium acetate (0.121 g, 0.89 mmol) is added to a suspension of (3aS,6aR)-2-benzyl-tetrahydrocyclopenta[c]pyrrole-1,3,5-trione (90 mg, 0.37 mmol) in ethanol (3 ml), followed by hydroxylamine hydrochloride (62 mg, 0.89 mmol) and water (1 ml). The reaction is heated to reflux for 1 hour and evaporated. The residue is partitioned between water and EtOAc, the organic phase is washed with brine, dried ($MgSO_4$) and evaporated to afford (3aR,6aS)-2-benzyl-tetrahydrocyclopenta[c]pyrrole-1,3,5-trione 5-oxime, MH+ 259.

A suspension of (3aR,6aS)-2-benzyl-tetrahydrocyclopenta[c]pyrrole-1,3,5-trione 5-oxime (86 mg, 0.33 mmol), platinum oxide (19 mg) and concentrated hydrochloric acid (0.2 ml) in ethanol (10 ml) is hydrogenated at 0.35 bar for 16 hours. The reaction mixture is filtered and the filtrate evaporated. The residue is partitioned between saturated aqueous sodium bicarbonate and EtOAc, the organic phase is washed with brine, dried (Na_2SO_4) and evaporated to afford a mixture of (3aR,5R, 6aS)-5-amino-2-cyclohexylmethyl-tetrahydro-cyclopenta[c]pyrrole-1,3-dione and (3aR,5S, 6aS)-5-amino-2-cyclohexylmethyl-tetrahydro-cyclopenta[c]pyrrole-1,3-dione, MH+ 251.

N,O-Bis(trimethysilyl)acetamide (33.5 µl, 0.20 mmol) is added to a suspension of (3aR,5R, 6aS)-5-amino-2-cyclohexylmethyl-tetrahydrocyclopenta[c]pyrrole-1,3-dione and (3aR,5S, 6aS)-5-amino-2-cyclohexylmethyl-tetrahydrocyclopenta[c]pyrrole-1,3-dione (68 mg, 0.27 mmol) in N,N-dimethylformamide (DMF) (1 ml) , followed 30 minutes later by 8-benzyloxy-5-R-oxiranyl-1H-quinolin-2-one (53 mg, 0.18 mmol). The reaction is heated at 90°C for 4 days. The solvent is evaporated and the residue purified by flash chromatography, eluting with EtOAc – 2% MeOH/EtOAc gradient to afford a mixture of (3aS,5R,6aR)-5-[R-2-(8-benzyloxy-2-oxo-1,2-dihydro-quinolin-5-yl)-2-hydroxy-ethylamino]-2-cyclohexylmethyl-tetrahydrocyclopenta[c]pyrrole-1,3-dione and (3aS,5S,6aR)-5-[R-2-(8-benzyloxy-2-oxo-1,2-dihydro-quinolin-5-yl)-2-hydroxy-ethylamino]-2-cyclohexylmethyltetrahydrocyclopenta[c]-pyrrole-1,3-dione, MH+ 544.

A suspension of (3aS,5R,6aR)-5-[R-2-(8-benzyloxy-2-oxo-1,2-dihydro-quinolin-5-yl)-2-hydroxy-ethylamino]-2-cyclohexylmethyltetrahydrocyclopenta[c]pyrrole-1,3-dione and (3aS,5S,6aR)-5-[R-2-(8-benzyloxy-2-oxo-1,2-dihydro-quinolin-5-yl)-2-hydroxy-ethylamino]-2-cyclohexylmethyltetrahydrocyclopenta[c]pyrrole-1,3-dione (29 mg, 0.05 mmol) and 10% Pd/C (11 mg) in MeOH (10 ml) is hydrogenated at 0.35 bar for 50 minutes. The reaction mixture is filtered through a Celite™ plug, washed with MeOH and the filtrate and washings are evaporated. The crude product is purified by preparative thin layer chromatography (multiple elutions with EtOAc) to afford a mixture of (3aS,5R,6aR)-2-cyclohexylmethyl-5-[R-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]tetrahydro-cyclopenta[c]pyrrole-1,3-dione and (3aS,5S,6aR)-2-cyclohexylmethyl-5-[R-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]tetrahydrocyclopenta[c]pyrrole-1,3-dione, MH+ 454.

Examples 2 to 4

These compounds are prepared using procedures analogous to those used in Example 1 using the appropriate amine.

Example 5

5-[R-2-((3aS,5R,6aR)-2-Butyloctahydrocyclopenta[c]pyrrol-5-ylamino)-1-hydroxyethyl]-8-hydroxy-1H-quinolin-2-one and

5-[R-2-((3aS,5S,6aR)-2-butyloctahydrocyclopenta[c]pyrrol-5-ylamino)-1-hydroxyethyl]-8-hydroxy-1H-quinolin-2-one

Methanesulfonyl chloride (1.93 ml, 24.9 mmol) is added to a cooled (0°C) solution of ((7R,8S)-8-hydroxymethyl-1,4-dioxa-spiro[4.4]non-7-yl)-methanol (*Tet. Lett.*, 2002, 43, 4947; 1.17 g, 6.22 mmol) and triethylamine (3.50 ml, 24.9 mmol) in dichloromethane (30 ml). The reaction is stirred for 2 hours at 0°C and then partitioned between dichloromethane and iced water. The organic phase is washed with 1M aqueous HCl, saturated aqueous $NaHCO_3$, brine, dried ($MgSO_4$) and evaporated to afford methanesulfonic acid (7R,8S)-8-methane-sulfonyloxymethyl-1,4-dioxaspiro[4.4]non-7-ylmethyl ester, MH+ 345.

A suspension of methanesulfonic acid (7R,8S)-8-methanesulfonyloxymethyl-1,4-dioxaspiro-[4.4]non-7-ylmethyl ester (0.250 g, 0.73 mmol) in n-butylamine (1 ml) is heated at 90°C for 3 hours. The reaction is evaporated and partitioned between EtOAc and 2M aqueous NaOH. The organic phase is washed with brine, dried ($MgSO_4$) and evaporated. The crude product is purified by flash chromatography, eluting with EtOAc to afford (3aR,6aS)-2-butylspiro[hexahydrocyclopenta[c]pyrrole-5(1H),2'-[1,3]dioxolane], MH+ 226.

A solution of (3aR,6aS)-2-butylspiro[tetrahydrocyclopenta[c]pyrrole-5(1H),2'-[1,3]dioxolane] (1.02 g, 45.3 mmol) in 0.5M aqueous HCl is stirred at ambient temperature for 16 hours. After washing with ether, 2M aqueous NaOH is added and the mixture is extracted with EtOAc. The organic phase is washed with brine, dried ($MgSO_4$) and evaporated to afford (3aS,6aR)-2-butylhexahydrocyclopenta[c]pyrrol-5-one, MH+ 182.

A suspension of (3aS,6aR)-2-butylhexahydrocyclopenta[c]pyrrol-5-one (0.467 g, 2.58 mmol), hydroxylamine hydrochloride (0.430 g, 6.19 mmol) and sodium acetate (0.842 g, 6.19 mmol) in ethanol (21 ml) and water (7 ml) is heated to reflux for 1 hour. The ethanol is evaporated and the residue partitioned between saturated aqueous $NaHCO_3$ and EtOAc. The organic phase is washed with brine, dried ($MgSO_4$) and evaporated to afford (3aS,6aR)-2-butylhexahydrocyclopenta[c]pyrrol-5-one oxime, MH+ 197.

Concentrated HCl (1.2 ml) is added to a solution of (3aS,6aR)-2-butylhexahydrocyclopenta[c]pyrrol-5-one oxime (0.306 g, 1.56 mmol) in ethanol, followed by platinum oxide (84 mg) and the suspension is hydrogenated at 0.35 bar for 16 hours. Further portions of platinum oxide (2 x 80 mg) are added until the reaction is complete after a total of 4 days. Water (20 ml) is added, the catalyst is filtered off and the filtrate evaporated to remove

ethanol. The residue is treated with 1M aqueous NaOH and extracted with ether. The organic phase is washed with water, brine, dried ($MgSO_4$) and evaporated to afford a mixture of (3aS,5R,6aR)-2-butyloctahydrocyclopenta[c]pyrrol-5-ylamine and (3aS,5S,6aR)-2-butyloctahydrocyclopenta[c]pyrrol-5-ylamine, MH+ 183.

N,O-Bis(trimethysilyl)acetamide (0.108 ml, 0.66 mmol) is added to a solution of (3aS,5R,6aR)-2-butyloctahydrocyclopenta[c]pyrrol-5-ylamine and (3aS,5S,6aR)-2-butyloctahydrocyclopenta[c]pyrrol-5-ylamine (0.159 g, 0.84 mmol) in DMF (1.5 ml), followed 30 minutes later by 8-benzyloxy-5-R-oxiranyl-1H-quinolin-2-one (0.171 g, 0.87 mmol). The reaction is heated at 90°C for 16 hours and the solvent is evaporated. The residue is triturated with EtOAc and the supernatant liquors diluted with hexane, left to evaporate and triturated with ether. The crude product is purified by flash chromatography (12:1 dichloromethane/MeOH – 1:1 MeOH/ammonia gradient elution) to afford a mixture of 8-benzyloxy-5-[R-2-((3aS,5R,6aR)-2-butyloctahydrocyclopenta[c]pyrrol-5-ylamino)-1-hydroxyethyl]-1H-quinolin-2-one and 8-benzyloxy-5-[R-2-((3aS,5S,6aR)-2-butyloctahydrocyclopenta[c]pyrrol-5-ylamino)-1-hydroxyethyl]-1H-quinolin-2-one, MH+ 476.

A mixture of 8-benzyloxy-5-[R-2-((3aS,5R,6aR)-2-butyloctahydrocyclopenta[c]pyrrol-5-ylamino)-1-hydroxyethyl]-1H-quinolin-2-one and 8-benzyloxy-5-[R-2-((3aS,5S,6aR)-2-butyloctahydrocyclopenta[c]pyrrol-5-ylamino)-1-hydroxyethyl]-1H-quinolin-2-one (38 mg, 0.08 mmol) and 10% Pd/C (20 mg) in MeOH (10 ml) is hydrogenated at 0.35 bar for 45 minutes. The reaction mixture is filtered through a Celite™ plug, washed with MeOH and the combined filtrate and washings evaporated. The residue is redissolved in MeOH and ether is added to precipitate a solid. The supernatant liquor is evaporated to afford a mixture of 5-[R-2-((3aS,5R,6aR)-2-butyloctahydrocyclopenta[c]pyrrol-5-ylamino)-1-hydroxyethyl]-8-hydroxy-1H-quinolin-2-one and 5-[R-2-((3aS,5S,6aR)-2-butyloctahydrocyclopenta[c]pyrrol-5-ylamino)-1-hydroxyethyl]-8-hydroxy-1H-quinolin-2-one, MH+ 386.

Examples 6 and 7

These compounds are prepared using procedures analogous to those used in Example 5 using the appropriate amine.

Example 8

5-[R-2-[R-(6,7-Dihydro-5H-[1]pyrindin-6-yl)amino]-1-hydroxyethyl]-8-hydroxy-1H-quinolin-2-one and

5-[R-2-[S-(6,7-dihydro-5H-[1]pyrindin-6-yl)amino]-1-hydroxyethyl]-8-hydroxy-1H-quinolin-2-one

Sodium metal (0.345 g, 15.0 mmol) is dissolved in ethanol (20 ml) and diethyl malonate (0.713 g, 4.70 mmol) is added, followed by a suspension of 2,3-bis(chloromethyl)pyridine hydrochloride (*Org. Process Res. Dev.*, 2002, 6, 938; 1.0 g, 4.70 mmol) in ethanol (15 ml) over 5 minutes. The reaction is heated to reflux for 5 hours, cooled to ambient temperature and filtered. The filtrate is evaporated, taken into water and extracted with ethyl acetate. The combined organic phases are washed with brine, dried ($MgSO_4$) and evaporated. The crude product is purified by flash column chromatography (3:1 - 2:1 isohexanes-EtOAc gradient) to afford 5,7-dihydro-[1] pyrindine-6,6-dicarboxylic acid diethyl ester, MH+ 264.

5,7-Dihydro-[1]pyrindine-6,6-dicarboxylic acid diethyl ester (0.953 g, 3.62 mmol) is taken into concentrated hydrochloric acid, heated to reflux for 4 hours and evaporated to afford 6,7-dihydro-5H-[1]pyrindine-6-carboxylic acid hydrochloride. δ_c (DMSO-d6) 33.9 (t), 34.5 (t) 41.2 (d), 124.8 (d), 140.1 (d), 140.8 (d), 141.2 (s), 158.4 (s), 175.2 (s)

Triethylamine (1.50 ml, 10.79 mmol) is added to a cooled (0°C) solution of 6,7-dihydro-5H-[1]pyrindine-6-carboxylic acid hydrochloride (1.00 g, 5.02 mmol) in acetone (8 ml) and water (1.6 ml), followed by dropwise addition of ethyl chloroformate (0.721 ml, 7.54 mmol) over 5 minutes. The reaction is stirred at 0°C for 50 minutes, then a solution of sodium azide (0.521 g, 8.04 mmol) in water (3 ml) is added. After 1.5 hours, the reaction is poured into brine and extracted with ether. The combined ether extracts are dried (Na_2SO_4) and evaporated. The residue is taken into toluene (40 ml) and gradually heated to 100°C until gas evolution ceases. The solvent is evaporated, the residue taken into 6N hydrochloric acid and heated to reflux for 16 hours. After evaporation, the crude hydrochloride salt is taken into MeOH and polymer supported trisamine (10 g) is added, followed by decolourising charcoal. The suspension is filtered through a Celite™ pad and the filtrate evaporated. The resultant material is purified by flash column chromatography (20:1 CH_2Cl_2-MeOH containing 1% triethylamine elution) to afford 6,7-dihydro-5H-[1]pyrindin-6-ylamine. δ_H 2.65 (1H dd J 15.9 5.1), 2.74 (1H dd J 16.6 5.1), 3.15 (1H dd J 16.1 7.0), 3.23 (1H dd J 16.6 7.0), 3.83 (1H m), 6.97 (1H dd J 6.9 4.8), 7.42 (1H d J 6.9), 8.28 (1H d J 4.8).

A suspension of 6,7-dihydro-5H-[1]pyrindin-6-ylamine (74 mg, 0.55 mmol) and 8-benzyloxy-5-R-oxiranyl-1H-quinolin-2-one (83 mg, 0.28 mmol) in 2-methoxyethyl ether

(1.5 ml) is degassed by bubbling argon for 5 minutes, then heated in a sealed tube at 160°C for 22 hours. The solvent is evaporated and the residue sonicated with MeOH and filtered to remove insoluble material. The filtrate is evaporated and purified by preparative LCMS (0-95% acetonitrile/water containing 0.1% trifluoroacetic acid gradient) to afford a mixture of 8-benzyloxy-5-{R-2-[R-(6,7-dihydro-5H-[1]pyrindin-6-yl)amino]-1-hydroxyethyl}-1H-quinolin-2-one bis(trifluoroacetate) and 8-benzyloxy-5-{R-2-[S-(6,7-dihydro-5H-[1]pyrindin-6-yl)amino]-1-hydroxyethyl}-1H-quinolin-2-one bis(trifluoroacetate), MH+ 428.

A suspension of 8-benzyloxy-5-{R-2-[R-(6,7-dihydro-5H-[1]pyrindin-6-yl)amino]-1-hydroxyethyl}-1H-quinolin-2-one trifluoroacetate and 8-benzyloxy-5-{R-2-[S-(6,7-dihydro-5H-[1]pyrindin-6-yl)amino]-1-hydroxyethyl}-1H-quinolin-2-one bis(trifluoroacetate) (22 mg, 0.03 mmol) and 10% Pd/C (10 mg) in ethanol (5 ml) is hydrogenated at 0.35 bar for 1.5 hours. The reaction mixture is filtered, evaporated and purified by preparative LCMS (0-95% acetonitrile/water containing 0.1% trifluoroacetic acid gradient) to afford a mixture of 5-{R-2-[R-(6,7-dihydro-5H-[1]pyrindin-6-yl)amino]-1-hydroxyethyl}-8-hydroxy-1H-quinolin-2-one bis(trifluoroacetate) and 5-{R-2-[S-(6,7-dihydro-5H-[1]pyrindin-6-yl)amino]-1-hydroxyethyl}-8-hydroxy-1H-quinolin-2-one bis(trifluoroacetate), MH+ 338.

Examples 9 to 29

These compounds are prepared using procedures analogous to those used in Example 8 using the appropriate amine.

Examples 30 to 33

These compounds are prepared using procedures analogous to those used in Example 1, using *R*-8-benzyloxy-5-oxiranyl-1H-quinolin-2-one and the appropriate amine.

Examples 34 to 36

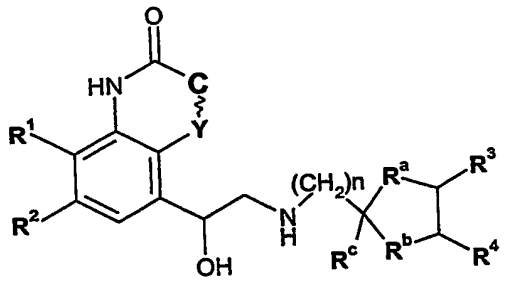
These compounds are prepared using procedures analogous to those used in Example 5, using *R*-8-benzyloxy-5-oxiranyl-1H-quinolin-2-one and the appropriate amine.

Examples 37 to 58

These compounds are prepared using procedures analogous to those used in Example 8, using *R*-8-benzyloxy-5-oxiranyl-1H-quinolin-2-one and the appropriate amine.

CLAIMS

1. A compound of formula I



I

in free or salt or solvate form, where

-C~Y- denotes $-CH_2-CH_2-$, -CH=CH- or $-CH_2-O-$;

one of R^1 and R^2 is hydroxy and the other is hydrogen;

n is an integer from 0 to 4;

R^a and R^b are independently $-CR^5R^6-$, $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$, -O-, $-CH_2-O-$, $-CH_2-O-CH_2-$, -S-, -SO-, $-SO_2-$, $-CH_2-S-$, $-CH_2-CH_2-S-$, $-CH_2-SO-$, $-CH_2-SO_2-$ or a bond;

R^c is hydrogen or C_1-C_{10}-alkyl optionally substituted by C_1-C_{10}-alkoxy, C_7-C_{15}-aralkyloxy, a C_5-C_{15}-carbocyclic group or by a 5- or 6-membered heterocyclic group wherein at least one of the ring atoms is nitrogen, oxygen or sulphur;

or when R^b is $-CR^5R^6-$, R^c and R^b form a C_5-C_{15}-carbocyclic group;

R^3 and R^4 form a 5- or 6-membered heterocyclic ring wherein at least one of the ring atoms is nitrogen, oxygen or sulphur, that ring being optionally substituted by halo, oxo, cyano, hydroxy, carboxy, aminocarbonyl, nitro, a C_5-C_{15}-carbocyclic group, C_7-C_{15}-aralkyl, C_1-C_{10}-alkyl optionally substituted by C_3-C_{10}-cycloalkyl, or C_1-C_{10}-alkoxy optionally substituted by C_3-C_{10}-cycloalkyl; and

R^5 and R^6 are independently hydrogen, C_1-C_{10}-alkyl or C_1-C_{10}-alkoxy, either of which being optionally substituted by a C_5-C_{15}-carbocyclic group.

2. A compound according to claim 1, where

-C~Y- is -CH=CH-;

one of R^1 and R^2 is hydroxy and the other is hydrogen;

n is 0 or 1;

R^a and R^b are both methylene;

R^c is hydrogen; and

R^3 and R^4 form a 5- or 6-membered heterocyclic ring wherein at least one of the ring atoms is nitrogen, oxygen or sulphur, that ring being optionally substituted by oxo, C_7-C_{15}-aralkyl or C_1-C_{10}-alkyl optionally substituted by C_3-C_{10}-cycloalkyl.

3. A compound according to claim 2, where
-C~Y- is -CH=CH-;
one of R^1 and R^2 is hydroxy and the other is hydrogen;
n is 0 or 1;
R^a and R^b are both methylene;
R^c is hydrogen; and
R^3 and R^4 form a 5- or 6-membered heterocyclic ring wherein at least one of the ring atoms is nitrogen, oxygen or sulphur, that ring being optionally substituted by oxo, C_7-C_{10}-aralkyl or C_1-C_4-alkyl optionally substituted by C_3-C_6-cycloalkyl.

4. A compound according to claim 1 substantially as herein described with reference to any one of the Examples.

5. A compound according to any one of the preceding claims for use as a pharmaceutical.

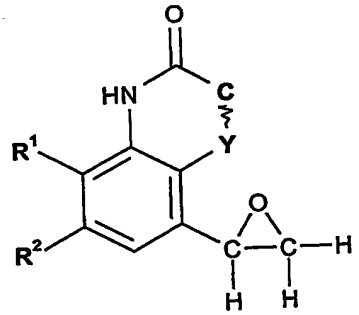
6. A pharmaceutical composition comprising a compound according to any one of the preceding claims, optionally together with a pharmaceutically acceptable carrier.

7. Use of a compound according to any one of claims 1 to 4 for the preparation of a medicament for the treatment of a condition which is prevented or alleviated by activation of the β_2-adrenoreceptor.

8. Use of a compound according to any one of claims 1 to 4 for the preparation of a medicament for the treatment of an obstructive or inflammatory airways disease.

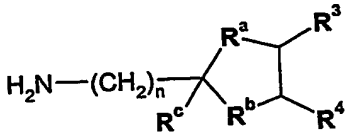
9. A process for the preparation of a compound of formula I in free or salt or solvate form comprising:

(i) (A) for the preparation of compounds of formula I reacting a compound of formula II



II

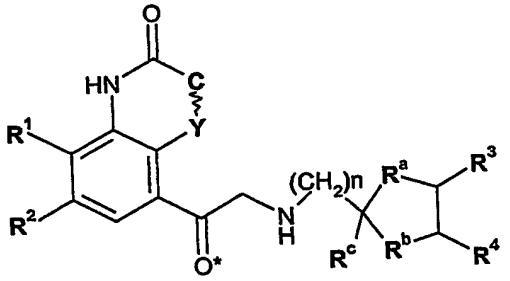
or a protected form thereof wherein -C-Y-, R^1 and R^2 are as hereinbefore defined, with a compound of formula III



III

or a protected form thereof wherein R^a, R^b, R^c, R^3, R^4 and n are as hereinbefore defined;

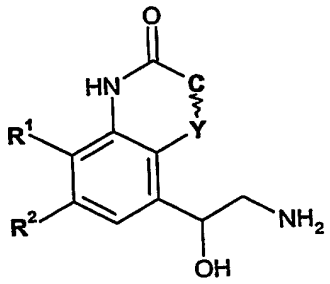
(B) reducing a compound of formula IV



IV

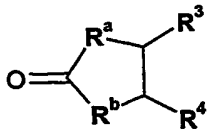
or a protected form thereof wherein -C~Y-, R^a, R^b, R^c, R^1, R^2, R^3, R^4 and n are as hereinbefore defined, to convert the indicated keto group into -CH(OH); or

(C) for the preparation of compounds of formula I where R^c is hydrogen and n is 0, reacting a compound of formula V



V

or a protected form thereof wherein -C~Y-, R^1 and R^2 are as hereinbefore defined, with a compound of formula VI

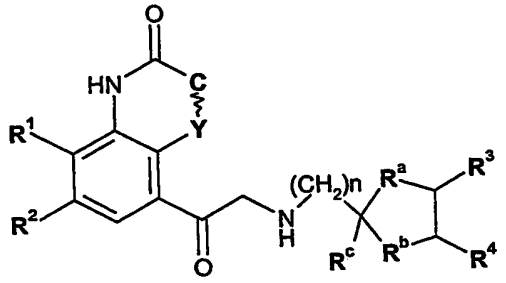


VI

or a protected form thereof wherein R^a, R^b, R^3 and R^4 are as hereinbefore defined; and

(ii) recovering the resultant compound of formula I in free or salt or solvate form.

10. A compound of formula IV



IV

in free or salt or solvate form, where

-C~Y- denotes $-CH_2-CH_2-$, -CH=CH- or $-CH_2-O-$;

one of R^1 and R^2 is hydroxy and the other is hydrogen;

n is an integer from 0 to 4;

R^a and R^b are independently $-CR^5R^6-$, $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$, -O-, $-CH_2-O-$, $-CH_2-O-CH_2-$, -S-, -SO-, $-SO_2-$, $-CH_2-S-$, $-CH_2-CH_2-S-$, $-CH_2-SO-$, $-CH_2-SO_2-$ or a bond;

R^c is hydrogen or C_1-C_{10}-alkyl optionally substituted by C_1-C_{10}-alkoxy, C_7-C_{15}-aralkyloxy, a C_5-C_{15}-carbocyclic group or by a 5- or 6-membered heterocyclic group wherein at least one of the ring atoms is nitrogen, oxygen or sulphur;

or when R^b is $-CR^5R^6-$, R^c and R^b form a C_5-C_{15}-carbocyclic group;

R^3 and R^4 form a 5- or 6-membered heterocyclic ring wherein at least one of the ring atoms is nitrogen, oxygen or sulphur, that ring being optionally substituted by halo, oxo, cyano, hydroxy, carboxy, aminocarbonyl, nitro, a C_5-C_{15}-carbocyclic group, C_7-C_{15}-aralkyl, C_1-C_{10}-alkyl optionally substituted by C_3-C_{10}-cycloalkyl, or C_1-C_{10}-alkoxy optionally substituted by C_3-C_{10}-cycloalkyl; and

R^5 and R^6 are independently hydrogen, C_1-C_{10}-alkyl or C_1-C_{10}-alkoxy, either of which being optionally substituted by a C_5-C_{15}-carbocyclic group.